

Visual Assessment of Coronary Artery Calcium in Non-ECG Gated Chest CT: A Multicenter Study

Hideya Yamamoto (✉ hideyayamamoto-circ@umin.ac.jp)

Yasuda Women's University <https://orcid.org/0000-0001-6357-1896>

Shinichiro Fujimoto

Juntendo University: Juntendo Daigaku

Chihiro Aoshima

Juntendo University: Juntendo Daigaku

Tohru Minamino

Juntendo University: Juntendo Daigaku

Takashi Fujii

JA Hiroshima General hospital

Shinichi Wakabaayshi

Suideikai Kajikawa Hospital

Yoji Urabe

Hiroshima Prefectural Hospital: Kenritsu Hiroshima Byoin

Hironori Ueda

Hiroshima Prefectural Hospital: Kenritsu Hiroshima Byoin

Eiji Kunita

Hiroshima city asa Hospital

Mitsunori Abe

Matsuyama Heart Center Yotsuba Clinic

Hiroshi Higashino

Matsuyama Heart Center Yotsuba Clinic

Research Article

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Abstract

Purpose: We sought to evaluate the visual measurements of coronary artery calcium (CAC) in chest CT without ECG gating, and to compare their predictive abilities for obstructive coronary artery disease (CAD).

Methods: We analyzed 163 subjects who underwent both coronary and chest CT examinations at 6 centers within 3 months. Agatston scores were calculated on standard ECG-gated scans and then classified into none (0), mild (1–99), moderate (100–400), and severe (>400) grades. Chest CT images were reconstructed with standard 5.0 mm axial slices. CAC in chest CT scans was measured using two methods: Weston score (sum of the assigned score of each vessel, range: 0–12) and number of slices showing CAC (Ca-slice#).

Results: We found excellent inter-observer agreement in the estimates of the Weston score and Ca-slice# ($R^2 = 0.913$ and 0.955 , respectively). When each of the two scores was divided into four levels, good agreement with the 4-grade Agatston score was observed (kappa value = 0.604 and 0.794 , respectively). Of the 155 patients remaining after excluding non-diagnostic studies, obstructed CAD, defined as the presence of $\geq 70\%$ stenosis on CT angiography, was found in 43 (27%). Receiver-operator characteristic curves of 4-grade hierarchies of Agatston score, Weston score, and Ca-slice# provided similar diagnostic powers to detect obstructed CAD (0.722 , 0.706 , and 0.718 , respectively).

Conclusion: The visual assessments of CAC detected by ECG non-gated chest CT scans were in good agreement with the ECG-gated Agatston score and also provided equivalent power to detect obstructive CAD.

This study was registered at UMIN-CTR (identifier: UMIN000039178; registered date; Jan 16, 2020)

Introduction

Coronary artery calcium score is associated with the prevalence of coronary artery disease (CAD) [1,2], mortality, and morbidity [3,4]. Coronary artery calcification (CAC) is screened by coronary computed tomography (CT) using the ECG-gated method, but is also often found incidentally on chest CT examinations. CAD is often complicated in patients with respiratory diseases such as lung cancer [5] or chronic obstructive pulmonary disease [6] because of the existing coronary risk factors of old age and cigarette smoking.

Several reports show that CAC on chest CT without ECG gate is in good agreement with the CAC score detected by the ECG-gated method [7-9]. In addition, visual estimation of CAC is expected to be an easy and feasible method for detecting CAD in subjects who undergo chest CT examinations. Several evaluation methods have been reported for the visual measurement of CAC in chest CT [10-13]; however, no established methods have yet been recommended.

In this multicenter study, we sought to validate the usefulness of visual estimation of CAC score in chest CT examinations without an ECG gated method, and to compare the predictive abilities of obstructive CAD using these visual CAC scoring systems in suspected CAD patients.

Methods

Study design

Between April and December 2020, patients who had an indication for coronary CT angiography were prospectively eligible for participation in this study to undergo simultaneous chest CT examination, but if patients had undergone chest CT examination to examine chest diseases performed within < 3 months before, these images were used for analysis. Patients were excluded from participation in the trial for the following reasons: body mass index (BMI) ≥ 35 kg/m² (because image quality was well guaranteed even in patients with a BMI of 30–35 kg/m², the criterion was amended from 30 kg/m²), known CAD, prior treated structure heart disease, status acute coronary syndrome or other urgent status, severe heart failure status, prior device implantation, and inadequate image quality. The study was performed at six centers in Japan (**Supplemental Table 1**). The ethical review board of Yasuda women's university and each participating institution approved the study protocol. Written informed consent was obtained from all patients. This study was registered at UMIN-CTR (identifier: UMIN000039178).

Coronary CT scan protocol and Agatston score

Coronary CT examinations were performed using new generation-type multidetector CT scanners according to each hospital's scan protocol (**Supplemental Table 1**). Prior to a contrast-enhanced scan, a non-contrast coronary CT scan was performed to detect the CAC. The following parameters were unified among hospitals: tube voltage, 120 kV; FOV, 25 cm. Thirty-five to 40 contiguous non-contrast coronary images of 2.5- (GE scanner) or 3.0- (Cannon scanner) mm thickness were obtained at 75% RR intervals. CAC scores on ECG-gated coronary CT were calculated using the conventional Agatston method in each hospital [1]. Agatston CAC was categorized into the following four classes: none = 0, mild = 1–99, moderate = 100–400, and severe >400 [14].

A contrast-enhanced coronary CT scan was performed according to the SCCT guideline [15]. If the patient's resting heart rate was > 65 beats per minute, a β -blocker (metoprolol 20–40 mg) was administered orally 60 min before the CT scan to avoid motion artifacts. The results of coronary CT were assessed in each hospital according to the criteria of the CAD-RADS reporting system [16]. Obstructive CAD was assessed by the presence of $\geq 70\%$ diameter stenosis in any coronary artery or $\geq 50\%$ diameter stenosis in the left main coronary artery [16].

Chest CT scan and evaluation of non-ECG gated CAC

Chest CT examinations without ECG gating were performed at each center using the same model as coronary CT examinations, including imaging of all lung fields from the apex to the base. The tube

voltage of the chest CT scan was uniformly set at 120 kV. Chest CT images were reconstructed with standard 5.0 mm axial slices.

Data analysis of CAC on chest CT

Chest CT images performed at each center were uploaded and saved as an anonymized DICOM format file in a specific "image storage system", installed on the cloud. Visual assessment of CAC on chest CT images of enrolled patients was performed by two skilled interpreters who were blinded to the patient information (SF and HH). Images were interpreted using free software (Sycorax DICOM viewer, CodeDynamix Co., Ltd), setting window levels of 35 to 50 Hounsfield units, and a window width of 350 to 500 Hounsfield units. Visual assessment was performed using two different methods. First, the Weston score was calculated according to a previous report [8-10]. The four coronary arteries (left main, left anterior descending, left circumflex, and right coronary) were scored for the extent of calcification using a 4-point scale: 0 = no calcium, 1 = one pixel of calcium, 2 = more than one pixel, but insufficient to classify as 3; and 3 = hard calcium, as evidenced by blooming artifact. We also used a unique evaluation method to count the number of slices containing CAC (Ca-slice#).

Interobserver agreement of each visual CAC measurement between the two readers was assessed in 40 randomly selected patients. **Figure 1** shows a representative case of coronary calcium images on chest CT examination.

Statistical analysis

The prevalence of obstructive CAD in the registered samples was estimated to be 25%. The required number of cases was calculated to be 95 when the area under the receiver-operator characteristic curves was estimated to be 0.71, the detection rate was 0.9, and the significance level was 0.05, which indicates the good predictive ability of obstructive CAD by the qualitative calcium evaluation method. Furthermore, we estimated the exclusion of test cases due to clinical reasons and imaging problems to be 10%, and set the target minimum number of cases to 106.

Categorical variables are reported as numbers (%). Continuous variables with a normal distribution are presented as mean \pm SD, and Agatston scores with a skewed distribution are presented as median and range. Agreements between two visually estimated measurements (Weston score and Ca-slice#) were tested using Pearson's correlation and Bland–Altman plots. Visual measurements were categorized into four classes (no, mild, moderate, and severe) depending on the Weston score. Then Agatston classes with the greatest frequency of scores were grouped in Weston classes. Agreements of score classes were expressed as Cohen's kappa statistics (95% confidence interval [CI]). A kappa value of >0.8 indicated excellent agreement, and a kappa value of 0.60 to 0.80 indicated good agreement.

Using receiver-operating characteristic (ROC) curves, c-statistics were determined for each calcium measurement to diagnose obstructive CAD. The optimal cut-off point was obtained from the Youden index [maximum (sensitivity+ specificity -1)]. Diagnostic measures were calculated, including sensitivity,

specificity, positive predictive value, negative predictive value, and accuracy. All statistical analyses were performed using JMP Pro Version 15 and SAS version 9.4.2 (SAS Institute, Cary, NC). Statistical significance was set at $P < 0.05$.

Results

Eligible patients

In this prospective multicenter study, 165 patients were initially eligible, and 2 were excluded because of known CAD or poor image quality. A total of 163 patients from six institutions were analyzed, including: Kajikawa Hospital (n=29), Juntendo University (n=40), JA Hiroshima Hospital (n=30), Hiroshima Prefectural Hospital (n=21), Hiroshima City Asa Hospital (n=12), and Matsuyama Heart Center (n=30). The average age was 68.4 ± 12.9 years, and 99 (61%) were men. Seventy-four (46%) patients complained of atypical chest pain and 28 (17%) complained of typical chest pain, whereas the remaining 61 (37%) patients had no chest symptoms. The study sample included 28 (17%) patients with cerebral infarction and eight (5%) patients with peripheral artery disease.

Chest CT examinations were prospectively performed in 105 patients (65%), and coronary CT scans were performed simultaneously. In the remaining 58 patients, chest CT examinations performed within 79 days before coronary CT [43 (27%) cases were performed within 1 to 7 days] were used for analysis. The Agatston score ranged from 0 to 3166 (median, 90). The prevalence of obstructive CAD was 43 (27% patients) (**Table 1**).

Interobserver agreements of each visual CAC measurement

There was an excellent interobserver agreement of each CAC measurement between the two observers ($R^2 = 0.913$ and 0.955 , Weston score, and Ca-slice#, respectively) (**Supplemental Figure 1**).

Agreements between visual CAC measurement and Agatston score

In the cohort, 20%, 32%, 22%, and 27%, had none (0), mild (1–99), moderate (100–400), and severe (>400) Agatston classes, respectively.

Figure 2 shows the distribution of Agatston classes by Weston score (0–12) (Panel A) and by Ca-slice# (0–17) (Panel B). Weston score was classified according to the hierarchy of the Agatston score, and graded as none, 0; mild, 1–4; moderate, 5–8; and severe, 9–12. The Weston score class was in good agreement with the Agatston score class [κ value = 0.604 (95% CI 0.511 – 0.696)] (Panel C). Similarly, Ca-slice# was graded as none = 0, mild = 1–4, moderate = 5–8, and severe = 9–17. Ca-slice# also showed good agreement with the Agatston score class [κ value = 0.794 (95% CI 0.720 – 0.869)] (Panel D).

Weston score classes agreed with Agatston score classes in 115 (71%) patients, but disagreed with the remaining 48 (29%) patients. The Ca-slice# classes agreed with Agatston score classes in 138 (85%)

patients, but disagreed with the remaining 25 (15%) patients. In each visual score, differences in clinical and imaging factors and CT machines were compared between the agreed and disagreed groups, but no significant parameters affecting their agreements were found.

Diagnostic performance for obstructive CAD using non-ECG gated calculated and visual estimated CAC scores

After excluding 8 patients with non-diagnostic studies, the diagnostic power was evaluated in 155 patients. Obstructed CAD was found in 43 patients (27%).

ROC analyses (**Figure 3**) showed comparisons of diagnostic performance in detecting obstructive CAD using three scores. The C-statistics of Agatston score, Weston score, and Ca-slice# were 0.750 (95% CI 0.646–0.831), 0.721 (95% CI 0.618–0.805), and 0.706 (95% CI 0.603–0.792), respectively ($p = 0.046$). Ca-slice# had a significantly lower c-statistic than the Agatston score (difference 0.044 [95% CI 0.008–0.080], $P = 0.016$).

In comparison, when divided into four classes, the c-statistics of the 4-grade hierarchies of Agatston score, Weston score, and Ca-slice# were 0.722 (95% CI 0.587–0.826), 0.706 (95% CI, 0.609–0.781), and 0.718 (95% CI 0.618–0.801), respectively, with no statistically significant differences ($P = 0.798$).

When each cutoff point was set at an Agatston score of 179, Weston score of 6, and Ca-slice# of 4, the sensitivity and specificity, respectively, for identifying obstructive CAD were 70% and 79% for Agatston score, 65% and 74% for Weston score, and 81% and 61% for Ca-slice#. When the cutoff point was set at a moderate class of each score, corresponding to an Agatston score of ≥ 100 , Weston score of ≥ 6 , and Ca-slice# of ≥ 4 , the sensitivity and specificity, respectively, for identifying obstructive CAD were 79% and 63% for Agatston score, 84% and 51% for Weston score, and 81% and 61% for Ca-slice# (**Table 3**).

Discussion

This study was conducted in collaboration at six centers in Japan to evaluate the usefulness of visual measurements of CAC detected by ECG non-gated chest CT scans. Our results showed that two visual measurements of CAC detected by chest CT scans were in good agreement with the ECG-gated Agatston score. The first method studied was the Weston score, which has already been reported, and the other is a simple method to count the number of slices in which calcium is reflected (Ca-slice#). These scores were in good agreement with the Agatston score obtained by the ECG-gate, using grading into four classes. In addition, the prediction rates of obstructive CAD detected on coronary CT angiography were equivalent to the Agatston score obtained by ECG-gate coronary CT.

Predictive ability of Weston score

ECG non-gated CAC scoring has become widespread as an easier screening method for CAD. The Weston score is a visual scoring method that includes segmented vessel-specific scoring using an ordinal scale of 0–3 [12]. Based on previous reports [8-10], Weston scores of ≥ 7 , which correspond to an Agatston

score of ≥ 400 , were defined as clinically significant. In a large multicenter cohort study, Weston scores of ≥ 7 indicated an elevation in predicting incident CAD in smokers [10]. Chandra et al. reported that the Weston score was categorized into four groups as follows: 0, 1–2, 3–7, and >8 [9]. Using this category criterion for our data, both classes showed moderate agreement [kappa value of 0.574 (95% CI 0.480–0.668)] (**Supplemental Figure 2**). However, the divisional levels of the moderate and severe groups were defined as 4 and 9, respectively, which were higher than those reported previously; this change also improved the kappa value from 0.574 to 0.706.

It has also been reported that the Weston score has a high diagnostic ability to detect obstructive CAD. For example, Bhatt et al reported that, for predicting prevalent CAD, c-statistics for the Weston and Agatston scores were 0.78 and 0.74, respectively [11], and West et al reported that a Weston score of 6 maximized the sensitivity and specificity at 89% and 76%, respectively [12]. Our data showed that the c-statistic for the Weston score was 0.750, and when the optimal cutoff point was set at 6, the sensitivity and specificity were 65% and 74%, respectively.

Predictive ability of Ca-slice#

In the present study, we proposed that Ca-slice#, counts of slices showing CAC as a new visual CAC measurement. The number of calcium slices is a highly reproducible and easily measurable index in chest CT taken with the same 5 mm slice, which is frequently used in clinical diagnosis. When Ca-slice# was graded into four classes, it also showed good agreement with the Agatston score class (kappa value = 0.794). In addition, although the predictive ability of Ca-slice# was inferior to the Agatston score, when both scores were graded into four classes, the predictive ability of Ca-slice# improved to be equivalent to the Agatston score.

Ca-slice#, as an index, may include several problems, such as the size of the heart according to the physique, concentration of calcium deposit, or anatomical features of the coronary artery. For example, the proximal part of the left anterior descending artery, which is a frequent site of calcification, runs in the horizontal direction, while the proximal part of the middle part of the right coronary artery runs in the axial direction. Therefore, calcification in the former is underestimated, while in the latter, it is overestimated. The diagnostic value is expected to increase further if these problems can be corrected.

Study limitations

First, this study was conducted in a cross-sectional manner to evaluate whether visual CAC scoring had predictive abilities to determine obstructive CAD on coronary CT angiography. The predictive power of hard outcomes was not assessed. Therefore, in the future, it will be necessary to verify the usefulness of visual evaluation for predicting long-term prognosis. Second, the diagnostic power of Ca-slice# was significantly lower than that of the Agatston score (c-statistics: 0.750 vs. 0.706, difference: 0.044, $P = 0.016$). However, when Ca-slice# was graded into four classes, it provided a good agreement with the Agatston score class (kappa value = 0.794). However, we could not find any significant parameters affecting the disagreements of score classes. To improve the diagnostic power, we plan to develop a new

scoring system using machine learning adding methods [17]. Finally, in this study, chest CT images were reconstructed with 5.0 mm axial slices. It is also necessary to measure the scores with different scan widths [18].

Conclusion

From our results in six centers, the visual assessments of CAC detected by ECG non-gated chest CT scan, Weston score, and Ca-slice# were in good agreement with the ECG-gated Agatston score. In addition, they also have a similar predictive power of obstructive CAD to the Agatston score.

Declarations

Acknowledgement

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Participating Institutions and Investigators

JA Hiroshima University; Shuji Tsujiyama, Hajime Shimodoi; Kajikawa Hospital; Eiji Imamura, Hiroki Sasaki; Matsuyama Heart Center Yotsuba Circulation Clinic, Fumitaka Kawajo, Aya Kashima; Hiroshima Prefectural Hospital; Naoya Mitsuba, Shogo Matsui, Masashi Takahashi, Satoshi Inada.

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Tables

Table 1 Patients' characteristics

Variables	<i>n</i> = 163
Age (yrs)	68.4 ± 12.9
Men	99 (61%)
Body mass index (kg/m ²)	24.3 ± 4.6
Hypertension, yes	108 (67%)
Dyslipidemia, yes	116 (59%)
Diabetes mellitus, yes	46 (29%)
Current smoker, yes	29 (18%)
Chest symptom, no/ atypical/ typical	61(37%)/ 74(46%)/ 28 (17%)
Cerebral infarction, yes	28 (17%)
Peripheral artery disease, yes	8 (5%)
Heart rate at rest ECG (bpm)	68.6 ± 12.0
Heart rate at coronary CT examination (bpm)	59.5 ± 9.2
Interval between coronary and chest CT scans	
0 days	105 (65%)
1-7 days	43 (27%)
8-79 days	15 (9%)
Reason for chest CT examination	
Prospectively eligible	98 (60%)
Previous chest screening	56 (56%)
Evaluation for proven lung disease	5 (3%)
Evaluation for proven thoracic vascular disease	4 (2%)

CT, computed tomography.

Table 2 Coronary CT examination

Variable	<i>n</i> = 163
Agatston score (median, range)	90 (11-426)
CAD-RADS grade ,n(%)	
0	23 (14%)
1	36 (22%)
2	40 (25%)
3	13 (8%)
4	33 (20%)
5	10 (6%)
N	8 (5%)
<i>n</i> = 155*	
Obstructive CAD [†]	43 (27%)

CAD, coronary artery disease; CAD-RADS, Coronary Artery Disease-Reporting and Data System *Of 13 patients in CAD-RADS 'N' group, 5 patients were included to obstructive CAD because of having one or more significant stenosis. †: defined as the presence of $\geq 70\%$ diameter stenosis in any coronary artery or $\geq 50\%$ diameter stenosis in the left main coronary artery.

Table 3 Diagnostic performance of each score to detect obstructed coronary artery disease

Variable	Optimal cutoff point	Sensitivity	Specificity	PPV	NPV	Accuracy
Agatston score	179	70%	79%	57%	87%	77%
Weston score	6	65%	74%	49%	85%	72%
Ca-slice#	4	81%	61%	44%	89%	66%
Agatston score 4 classes	\geq moderate (100)	79%	63%	45%	89%	67%
Weston score 4 classes	\geq moderate (4)	84%	51%	40%	89%	60%
Ca-slice# 4 classes	\geq moderate (4)	81%	61%	44%	89%	66%

Ca-slice#, number of slices showing coronary artery calcium; NPV, negative predictive value; PPV, positive predictive value

Figures

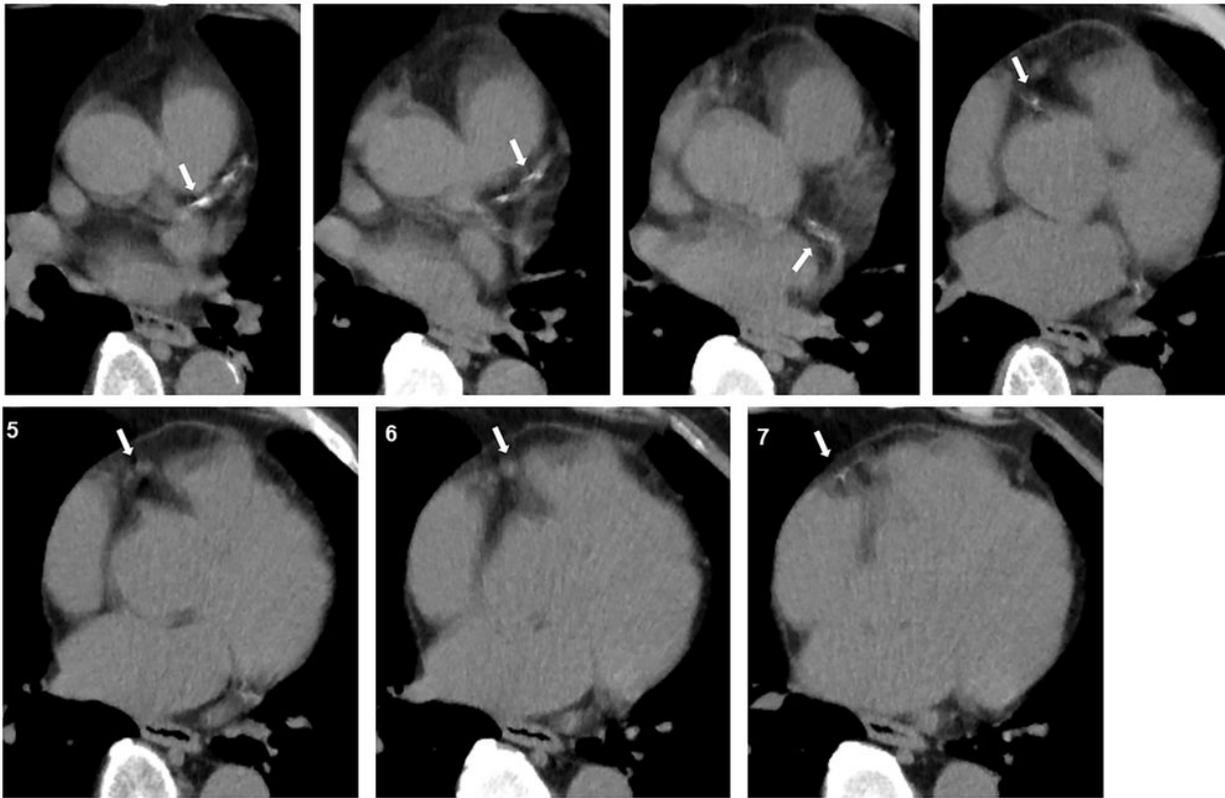


Figure 1

A representative case. A 69-year-old asymptomatic man had hypertension and a history of cerebral infarction. On an ECG gating scan, his Agatston score was 215 (defined as moderate class). On a non-gating scan, coronary calcium deposits (white arrows) were detected in seven slices (Ca-slice# = 7, moderate class), and Weston scores were summed up to 7 (left anterior descending artery, 3; left circumflex artery, 2; and right coronary artery, 2).

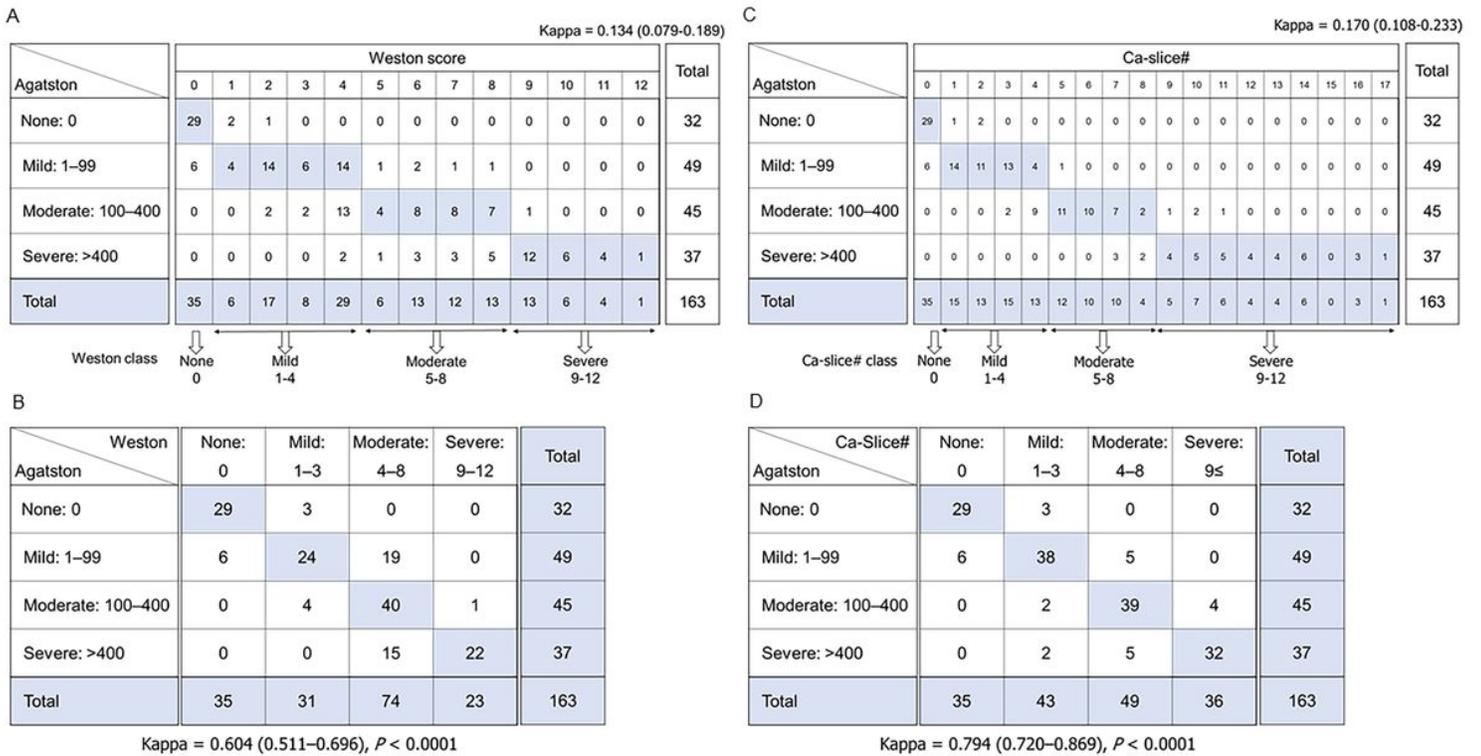


Figure 2

Agreements of classes between each visual score and Agatston score. Distribution of Weston and Agatston score classes (A). Weston scores were classified according to the Agatston score class with the greatest frequency; good agreement of classes was thereby obtained between the Weston and Agatston scores (B). Distribution of the total number of slices containing calcium (Ca-slice#) and Agatston score classes (C). Similarly, Ca-slice# scores were classified by grouping the Agatston score class with the greatest frequency as none (0), mild (1-4), moderate (5-8), and severe (9-12). Good agreement of classes was obtained between the Ca-slice# and Agatston score (D).

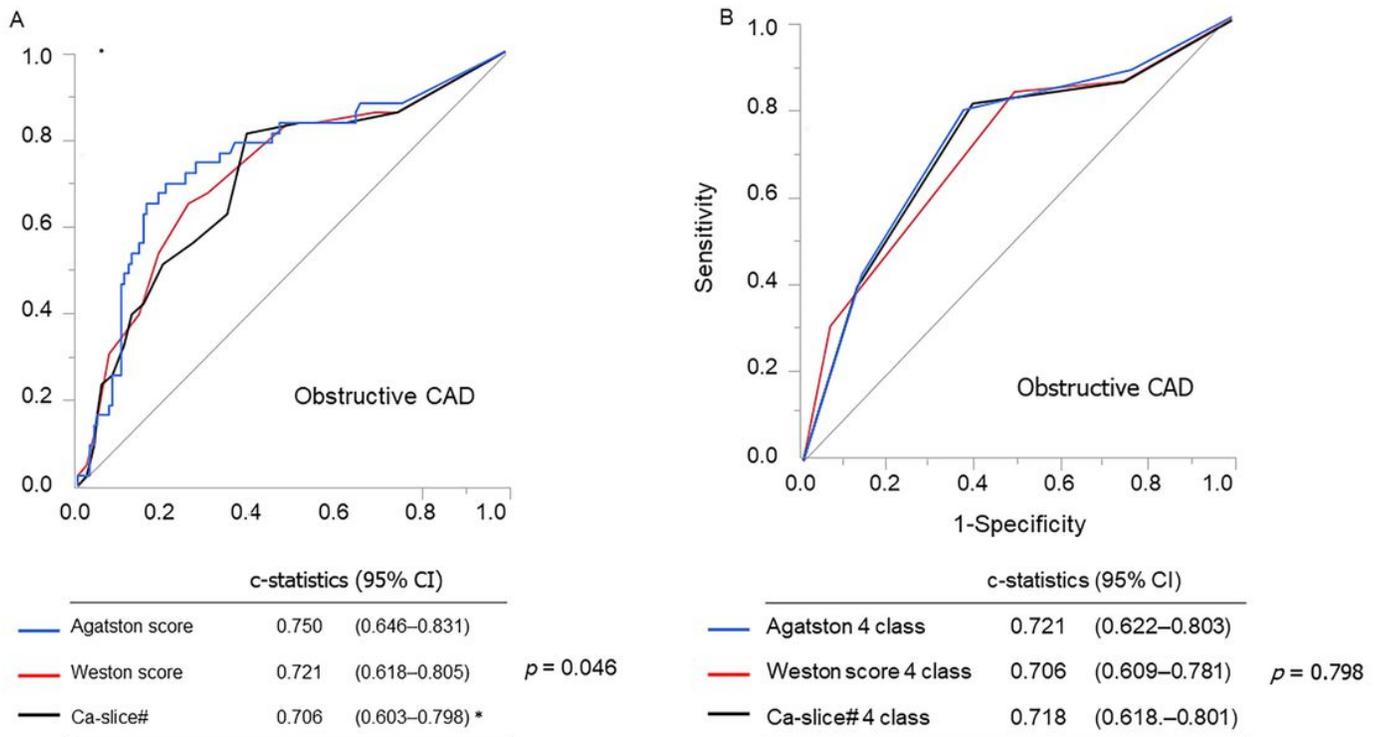


Figure 3

Receiver-operator characteristics analyses to detect obstructive CAD. Obstructed CAD was found in 43 (27%) of 155 patients. Comparison of c-statistics of Agatston score, Weston score, and Ca-slice# (A). Comparison of c-statistics of classes of Agatston score, Weston score, and Ca-slice# (B). *C-statistics were significantly lower than those from the Agatston score (difference, 0.044; 95% CI 0.008–0.080; $P = 0.016$).

Supplementary Files

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